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# EFFECTS OF COLD EXPOSURE UPON THE ACTION OF THERAPEUTIC DRUGS: PART II

James Y. P. Chen
H. C. Bergman

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ARCTIC AEROMEDICAL LABORATORY

AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
FORT WAINWRIGHT, ALASKA

## NOTICES



This research was conducted in accordance with the "Principles of Laboratory Animal Care" of the National Society for Medical Research.

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## FOREWORD

This is a second report, prepared under Contract AF 41(609)-2683 (Project 8241, Task 824102), with the Life Sciences Department of Space and Information Systems Division, North American Aviation, Inc., Downey, California. The report covers research carried on from November 1964 to November 1965. Air Force program monitor is Dr. Horace F. Drury, ALR, Arctic Aeromedical Laboratory.

Technical assistance in research for this report was provided by James E. Fitzgerald and Leilani C. Chu.

This technical report has been reviewed and is approved.

Horace F. Drury
HORACE F. DRURY
Director of Research

## ABSTRACT

In rats acutely exposed to cold as compared to room temperature, the toxic responses to parenteral injections of meperidine hydrochloride, of dextroamphetamine sulfate and of prochlorperazine ethanesulfonate were invariably greater in cold than at room temperature. With further experiments an even greater increase was noted in the acute oral toxicity of prochlorperazine dimaleate at 4° C; the acute oral toxicity of this drug was 144 times greater at 4° C than at room temperature. This large difference in toxicity appeared to be an additive effect of the inherent hypothermic action of the drug and of the temperature-lowering action in the cold environment. Tests with larger animals, monkeys and dogs, indicated that the differences in toxicity between the room temperature and cold environments were not as great as in rats. The ability of large animals to retain body heat in the cold for a longer time than rats can may have contributed to the lesser effect. The results with monkeys injected with prochlorperazine in increasing dosage may have revealed the possibility of a tolerance development to the drug. Dextroamphetamine sulfate was about equally effective at either environment in inhibiting sleep in monkeys induced with pentobarbital. The tranquilizing effect of prochlorperazine, as shown by avoidance behavior in monkeys subjected to a mild electric shock, was found to be about the same at 4° C as at room temperature. In dogs, injections of prochlorperazine at room temperature were about as effective as at 4° C in preventing emesis by an emetic dose of apomorphine.

I

# INTRODUCTION

This report is a continuation of the previous investigations on the toxicity and efficacy of drugs in acutely cold-exposed animals compared with controls at normal room temperature (1). In the previous report, it was shown that the toxicity of morphine and of pentobarbital increased significantly in animals acutely exposed to cold. The median effective hypnotic dose of pentobarbital was no different in either environment. It was found, however, that the median effective analgesic dose of morphine sulfate was about 72% lower in a cold temperature ($4^{\circ} \pm 1^{\circ}$ C) than at room temperature ($22^{\circ}$ to $25^{\circ}$ C). The present investigation was conducted with another analgesic (meperidine), a tranquilizer (prochlorperazine), and a central nervous system stimulant (dextroamphetamine).

II

# MATERIALS AND METHODS

## General Experimental Conditions

The experiments were conducted with Wistar albino rats (130 to 200 gm), mongrel dogs (4 to 12 kg), and with five female rhesus monkeys (4 to 6 kg). (Monkeys were supplied by the Air Force Systems Command, Aerospace Medical Division, School of Aviation Medicine, Brooks Air Force Base, Texas.)

The test procedure usually involved the determination of an effective or a toxic dose of the test drugs at normal ambient temperatures of $22^{\circ}$ to $25^{\circ}$ C. Parallel experiments were then conducted with a second group of animals kept in a specially constructed walk-in cold room maintained at $4^{\circ} \pm 1^{\circ}$ C. All animals studied in the cold room were individually caged to prevent huddling or excessive movements. After the animals were placed in the cold room, the test drugs were administered to cold-exposed rats 60 to 120 minutes later and to dogs and monkeys after 180 minutes.

Acute toxicity of the test drugs was based on the mortality response over a 24-hour period. Other phenomena were observed for two to eight hours, depending on the nature of the test. Compazine (prochlorperazine dimaleate and prochlorperazine ethanesulfonate) was supplied by Smith, Kline, and French Laboratories.

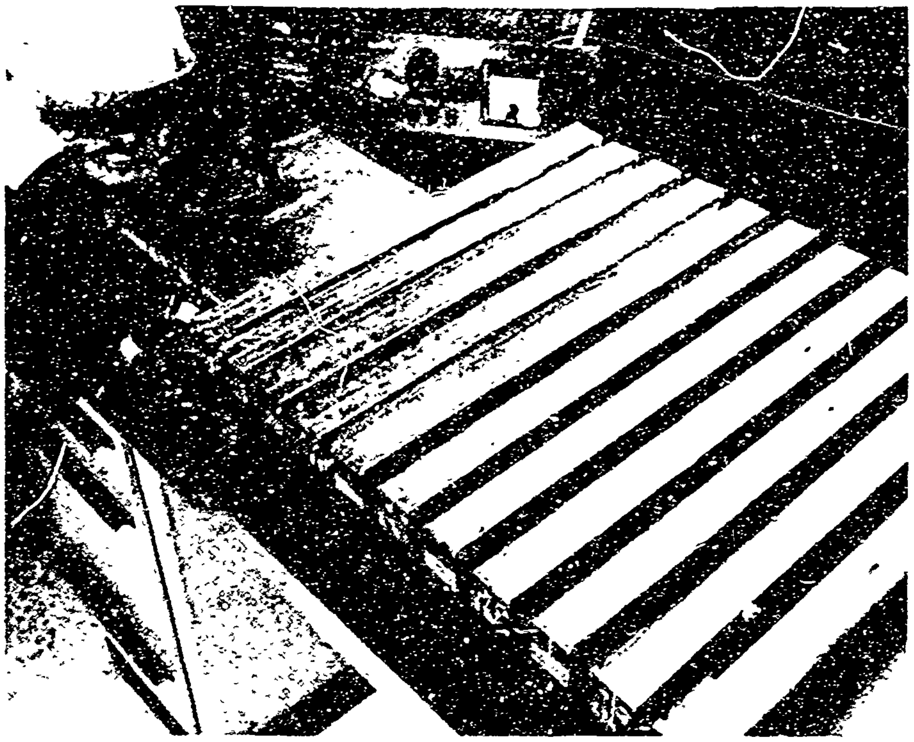
Determination of Pharmacologic Activity

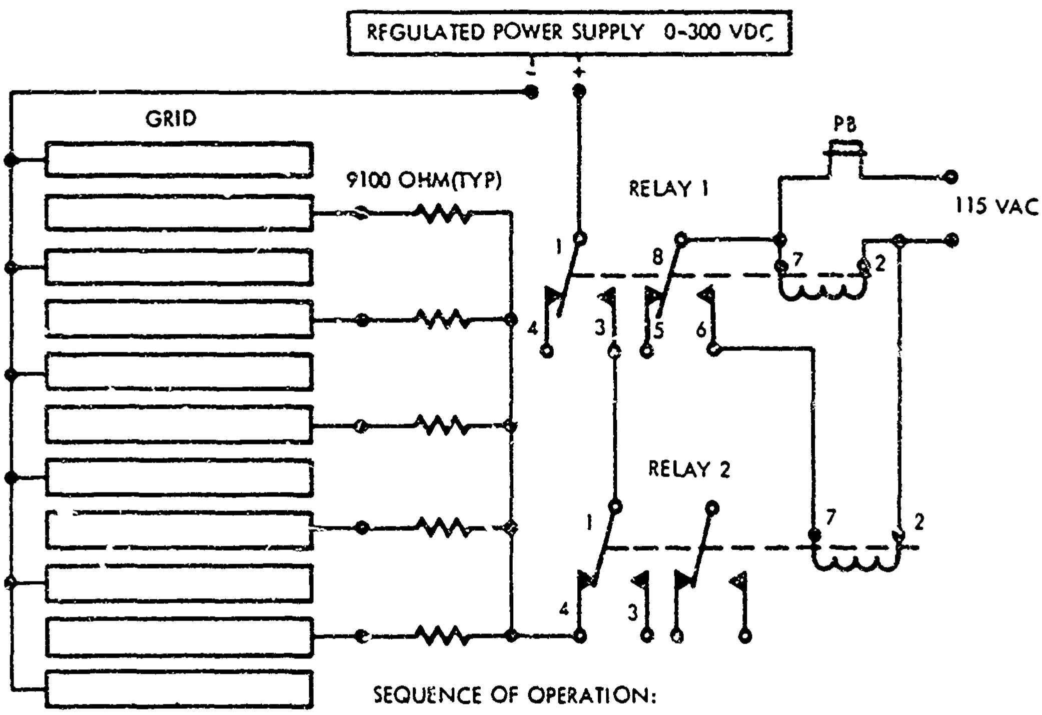
Analgesic action of meperidine (Demerol). The tail-pinching method of Chen (2) was used as described in the previous report (1). In essence this involved pinching the tail of a rat with a special forceps to evoke vocalization and then marking this point. The pinching was repeated 0.5 cm above this point several times after the test material had been injected. Analgesic potency was graded by the amount of pressure required to elicit a squeal from the animal. The responses were graded as + with one notch of pressure, ++ with the second notch engaged, and ++++ for the fourth notch.

Effect of prochlorperazine (Compazine) and dextroamphetamine (Dexedrine) on the sedative and hypnotic action of pentobarbital. The time for loss and recovery of righting reflexes was tested in rats after intraperitoneal injection of pentobarbital or pentobarbital and the test drugs. For rats, the ability to hang on to a smooth plastic plate inclined at 24 degrees was taken as a measure of loss or recovery of righting reflexes. Male rats, 130 to 180 gm, were injected intraperitoneally with either pentobarbital, pentobarbital plus dextroamphetamine sulfate, or a pentobarbital solution and a separate prochlorperazine solution. The reason for separate solutions in the latter group was that a precipitate developed when a pentobarbital solution was mixed with a prochlorperazine solution. It was later found that a pH change towards alkalinity was responsible for this incompatibility. Experiments were performed at room temperature and at 4° C. Although 16 sets of rats were used, no consistent pattern developed. Different groups reacted variably to the same injection doses. The groups placed in a temperature of 4° C were so sensitive to pentobarbital that they did not survive hypnotic doses of 20 to 30 mg/kg. Doses of 15 mg/kg gave equivocal responses in different groups to the pentobarbital alone and the drug combinations. Thus it was not possible to obtain quantitative evaluation of either dextroamphetamine sulfate or prochlorperazine in rats.

With monkeys, the response to a movement or a noise and the general appearance of the animal were observed as a measure of sedative action.

Tranquilization or cerebral stimulation. Attempts to obtain unequivocal data on the movements of animals injected intraperitoneally with saline, prochlorperazine, or dextroamphetamine while on jiggle boards (Lehigh Valley Electronics, Fogelsville, Pa.) were unsuccessful. Apparently the animals (mice, rats, and guinea pigs) were disturbed by the movement of their cage floor and by the noise of the counting device. In most instances the animals stopped moving after becoming conditioned to the apparatus. This happened in spite of large doses of dextroamphetamine. Because the data were so inconsistent, no further discussion of the jiggle board experiments will be made in this report.






SEQUENCE OF OPERATION:

1. PRESS PUSHBUTTON (PB)
2. RELAY 1 CLOSES, SENDING CURRENT TO GRID AND ENERGIZING COIL OF RELAY 2
3. TEN MILLISECONDS AFTER CONTACTS OF RELAY 1 SEND CURRENT TO GRID, RELAY 2 OPENS AND CURRENT TO GRID STOPS
4. PUSH BUTTON RELEASE RESTORES RELAY 1 BEFORE RELAY 2 BY NATURE OF CONTACT ADJUSTMENT; THERE IS NO SECONDARY PULSE UPON RELEASE

FIGURE 1

Electric Shock Device for Monkeys

Prochlorperazine and apomorphine emesis. Male dogs (7 to 11 kg) were fed one-half can of dog food. Each dog was injected intraperitoneally with a dilute saline solution of prochlorperazine (Compazine Injection) either at room temperature or after three hours at 4° C. Exactly one hour after the prochlorperazine injection, the dogs were injected intramuscularly with 0.2 mg of apomorphine hydrochloride in 0.1 ml of saline. The dogs were observed for vomiting during a two-hour interval; however, vominting occurred after two to seven minutes or not at all.

Tranquilization with prochlorperazine. Female rhesus monkeys (4.2 to 5.9 kg) were placed in a cage on a grid attached to a power supply to produce an electric shock up to 300 volts (Figure 1). (The electric shock device was designed and built by E. R. Schnauss of the Instrument Project of Life Sciences, S&ID.) The monkeys were injected intraperitoneally with various amounts of prochlorperazine (Compazine Injection) in 1 ml of saline per kg either at room temperature or after 1.5 to 2 hours at 4° C. The monkeys were stimulated with random shocks at increasing voltage until there was a definite avoidance behavior as evidenced by an attempt to get off the grid or by vocalization. Most avoidance occurred with 80 volts or less. With severe tranquilization there was no response between 150 and 300 volts. Figures 2 and 3 illustrate the behavior difference in a monkey before and after treatment with prochlorperazine.

FIGURE 2

Monkey Prior to Injection of Prochlorperazine

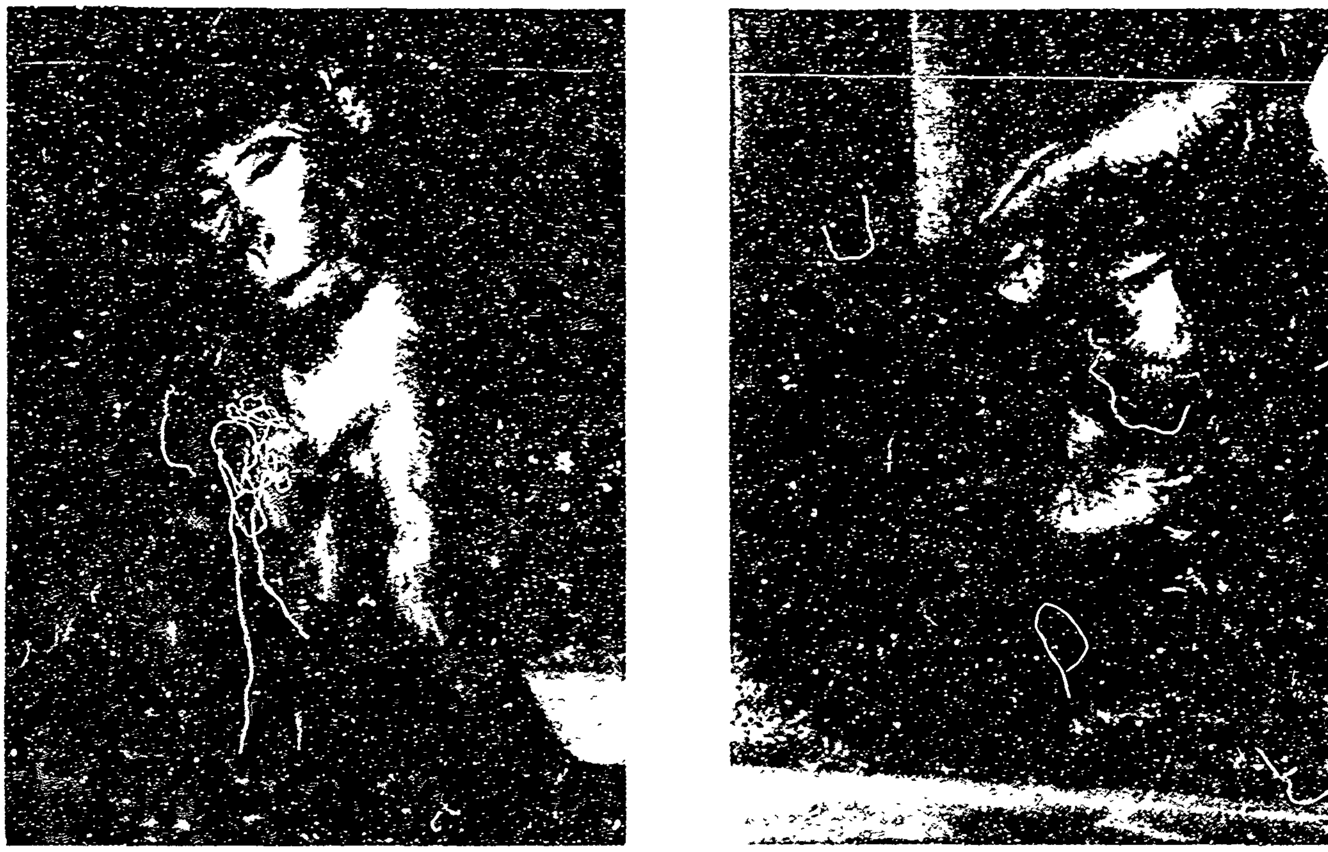


FIGURE 3

Response of Monkey to a Tranquilizing Dose of Prochlorperazine

Temperature response to oral prochlorperazine dimaleate. The stomachs of male rats were intubated with a suspension of prochlorperazine dimaleate in gum arabic and water or with the vehicle only. The suspension was prepared by placing the prochlorperazine dimaleate and gum arabic (one-quarter the weight of the drug) in a mortar. The solids were mixed and titrated with small volumes of water to a fine paste. This was diluted to contain the required dose in 1 ml (10 ml per kg of rat). Rectal temperatures were taken hourly with a Yellow Springs resistance thermometer. Groups of six to seven rats each were tested at normal ambient room temperature and at $4^{\circ} \pm 1^{\circ}$ C, where the drug was administered one hour after placing the rats in the cold environment.

## III

## RESULTS

### Meperidine Hydrochloride

In rats, the acute subcutaneous $LD_{50}$ of meperidine hydrochloride (Demerol) at $22^{\circ}$ to $24^{\circ}$ C was found to be 125 mg/kg; at $4^{\circ}$ C it was 70 mg/kg

as shown in Figure 4. It will be seen that meperidine was about twice as toxic to rats at 4° C than at normal ambient room temperature.

Figure 5 illustrates the responses to subcutaneous analgesic doses of meperidine hydrochloride in rats at 21° and 4° C. Comparison of equivalent responses shows that meperidine was 2.5 to 5 times more effective at 4° C than at 21° C.

Taking an average analgesic dose of 20 mg/kg at 21° C and the related $LD_{50}$ of 125 mg/kg, a therapeutic index ($LD_{50}$/ED) of 6.3 is obtained. Likewise, at 4° C a therapeutic index of 8.8 (70/8) is found. It must be remembered, however, that an effective dose at 4° C is lower than at room temperature.

## Dextroamphetamine Sulfate

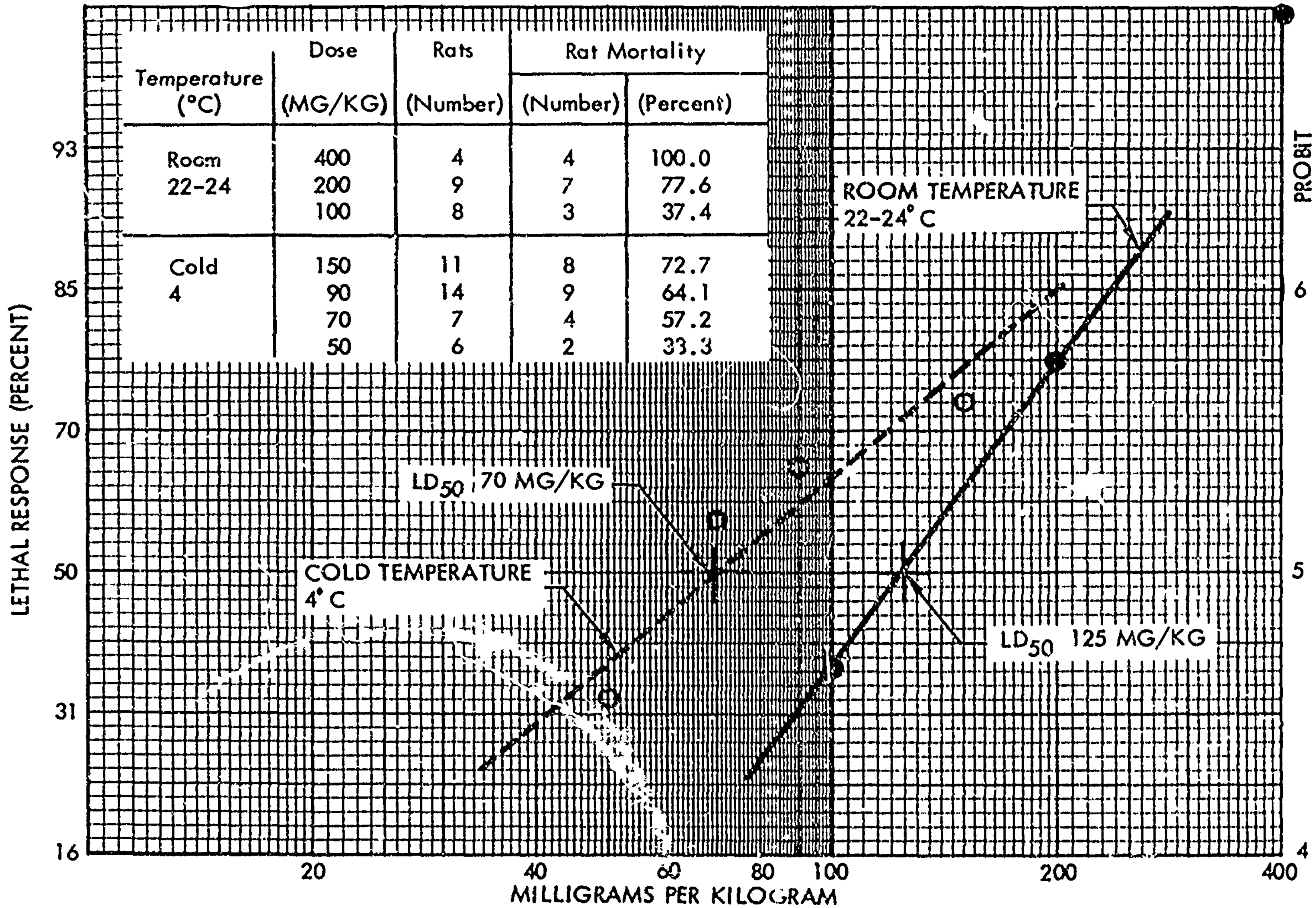
Figure 6 shows the results obtained with injections of dextroamphetamine sulfate into rats at 23° and 4° C. The acute subcutaneous $LD_{50}$ was 240 mg/kg at 23° C as compared to 32 mg/kg at 4° C. Dextroamphetamine was 7.5 times more toxic for rats subjected to 4° C than those at room temperature environment.

Toxicity tests results with dogs are presented in Table I. After dogs were kept three hours at 4° C, intraperitoneal injections of 50 mg/kg of dextroamphetamine sulfate killed two of four dogs within 24 hours. At 23° C, doses of 50 mg/kg killed one of two dogs, and higher doses killed all six dogs. It appears that in animals larger than rats the acute toxicity of dextroamphetamine may not differ greatly at room or cold environments.

TABLE I

Intraperitoneal Injection of Dextroamphetamine Sulfate Into Dogs at 23° and 4° C

| Temperature (°C) | Dose (mg/kg) | No. of Dogs Used | Mortality |
|---|---|---|---|
| Room 23 | 200 | 4 | 4 |
| | 100 | 2 | 2 |
| | 50 | 2 | 1 |
| Cold 4 | 50 | 4 | 2 |




| Temperature (°C) | Dose (MG/KG) | Rats (Number) | Rat Mortality (Number) | Rat Mortality (Percent) |
|---|---|---|---|---|
| Room 22-24 | 400 | 4 | 4 | 100.0 |
| | 200 | 9 | 7 | 77.6 |
| | 100 | 8 | 3 | 37.4 |
| Cold 4 | 150 | 11 | 8 | 72.7 |
| | 90 | 14 | 9 | 64.1 |
| | 70 | 7 | 4 | 57.2 |
| | 50 | 6 | 2 | 33.3 |

FIGURE 4

Lethal Response of Rats to Meperidine Hydro- ,oride , , ( . ) at Room Temperature and at $4^{o}$ C

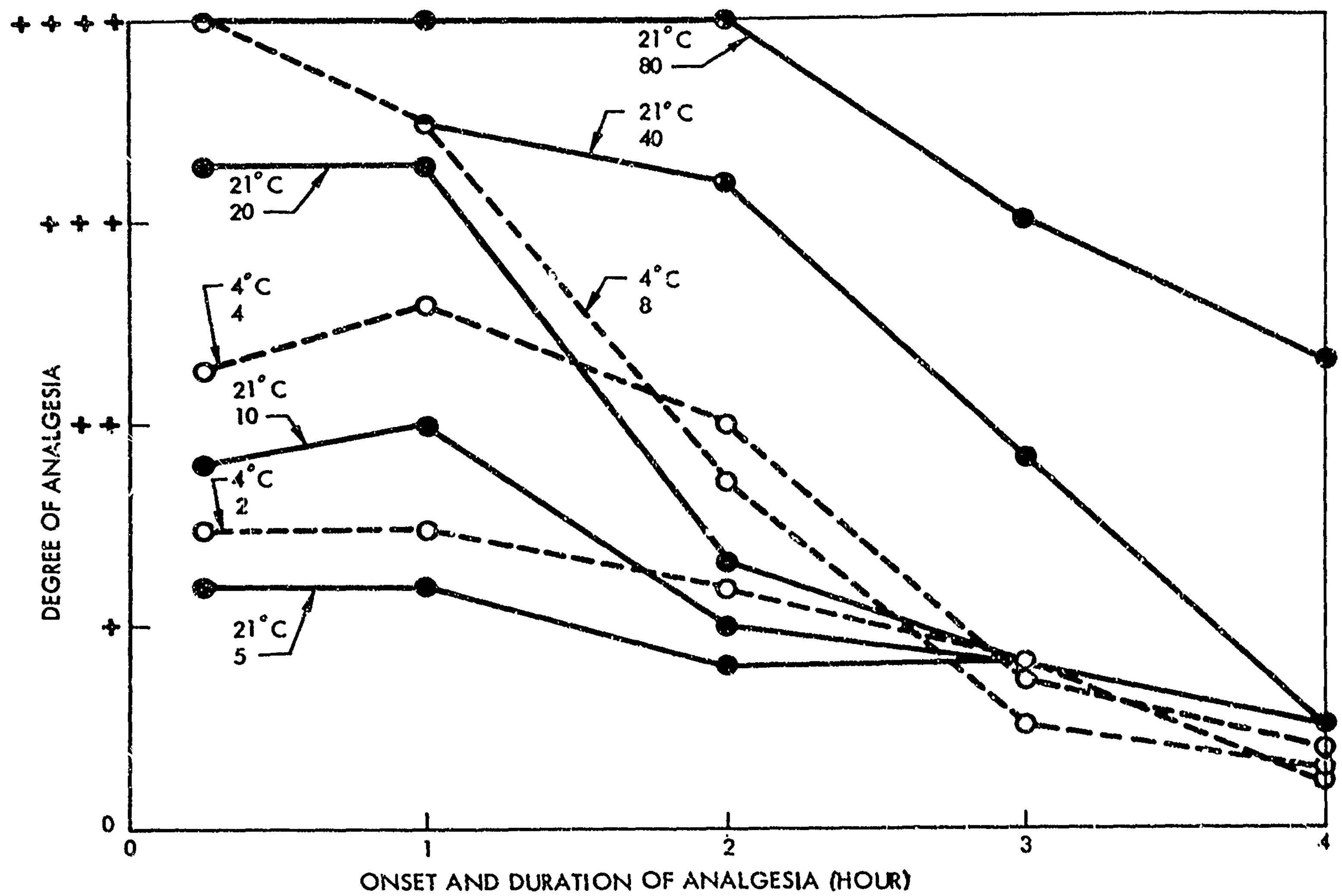
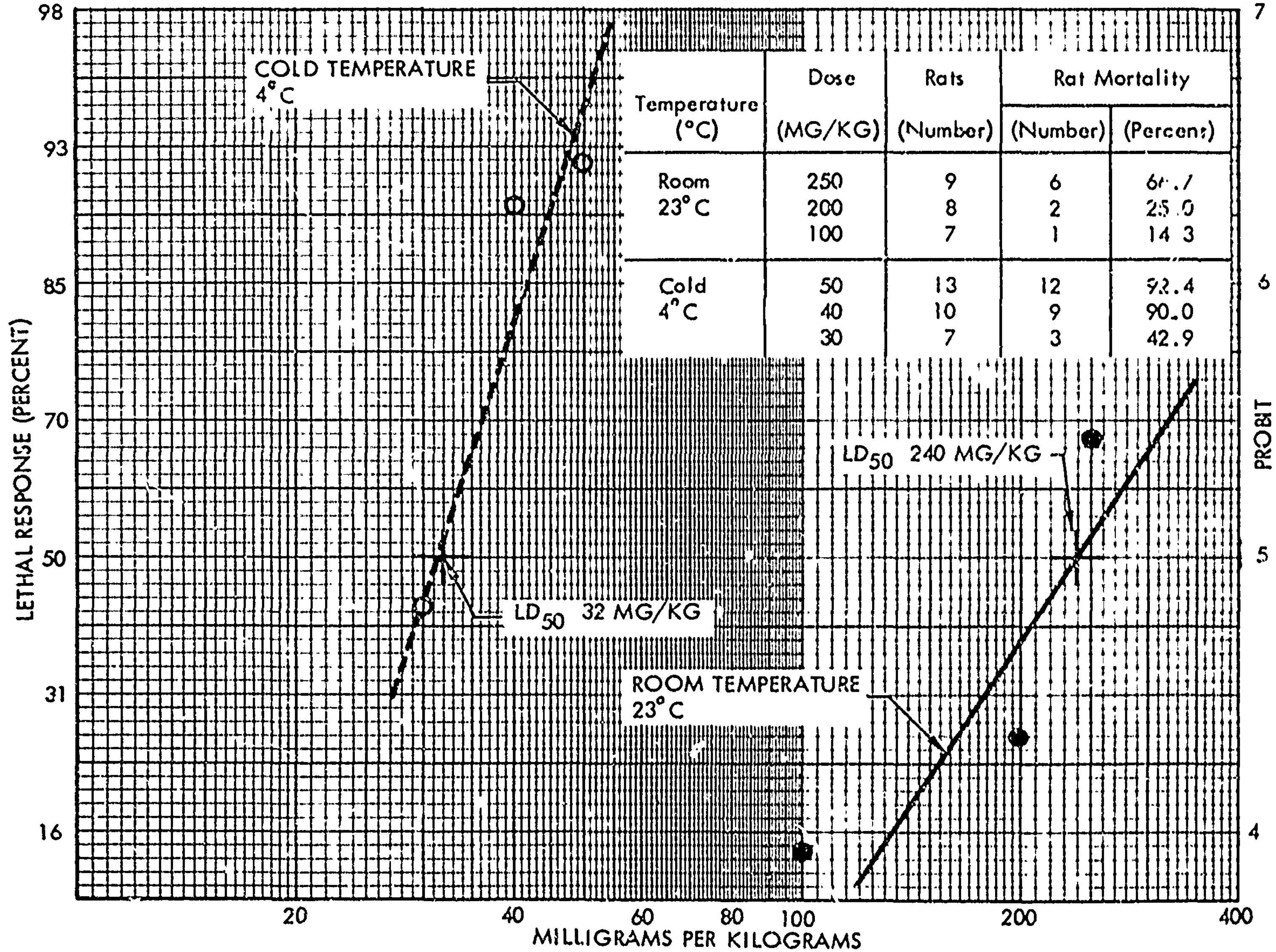



FIGURE 5

Analgesic Effect on Rats of Subcutaneous Meperidine Hydrochloride at Room Temperature and at 4° C --- Doses in mg/kg




| Temperature (°C) | Dose (MG/KG) | Rats (Number) | Rat Mortality (Number) | Rat Mortality (Percent) |
|---|---|---|---|---|
| Room 23°C | 250 | 9 | 6 | 66.7 |
| | 200 | 8 | 2 | 25.0 |
| | 100 | 7 | 1 | 14.3 |
| Cold 4°C | 50 | 13 | 12 | 92.4 |
| | 40 | 10 | 9 | 90.0 |
| | 30 | 7 | 3 | 42.9 |

FIGURE 6

Lethal Response of Rats to D-Amphetamine (S.C.) at Room Temperature and at 4° C

The results of intraperitoneal injections of pentobarbital or a mixture of pentobarbital and dextroamphetamine sulfate into monkeys at room temperature and three hours after placing the monkeys in a temperature of 4° C are shown in Table II. The term "sleeping" as given in the table is defined as a drowsy appearance, difficulty in arousing to a touch, or unconsciousness. With the high dose of 40 mg/kg, the sleeping response was marked and persisted for two to four hours. With the 20 mg/kg and the 15 mg/kg doses, the response was lighter and lasted for about one hour. It appeared that 0.2 mg/kg of dextroamphetamine along with 15 mg/kg of pentobarbital was equally effective at both 23° and 4° C in preventing sleep when injected intraperitoneally into monkeys.

TABLE II

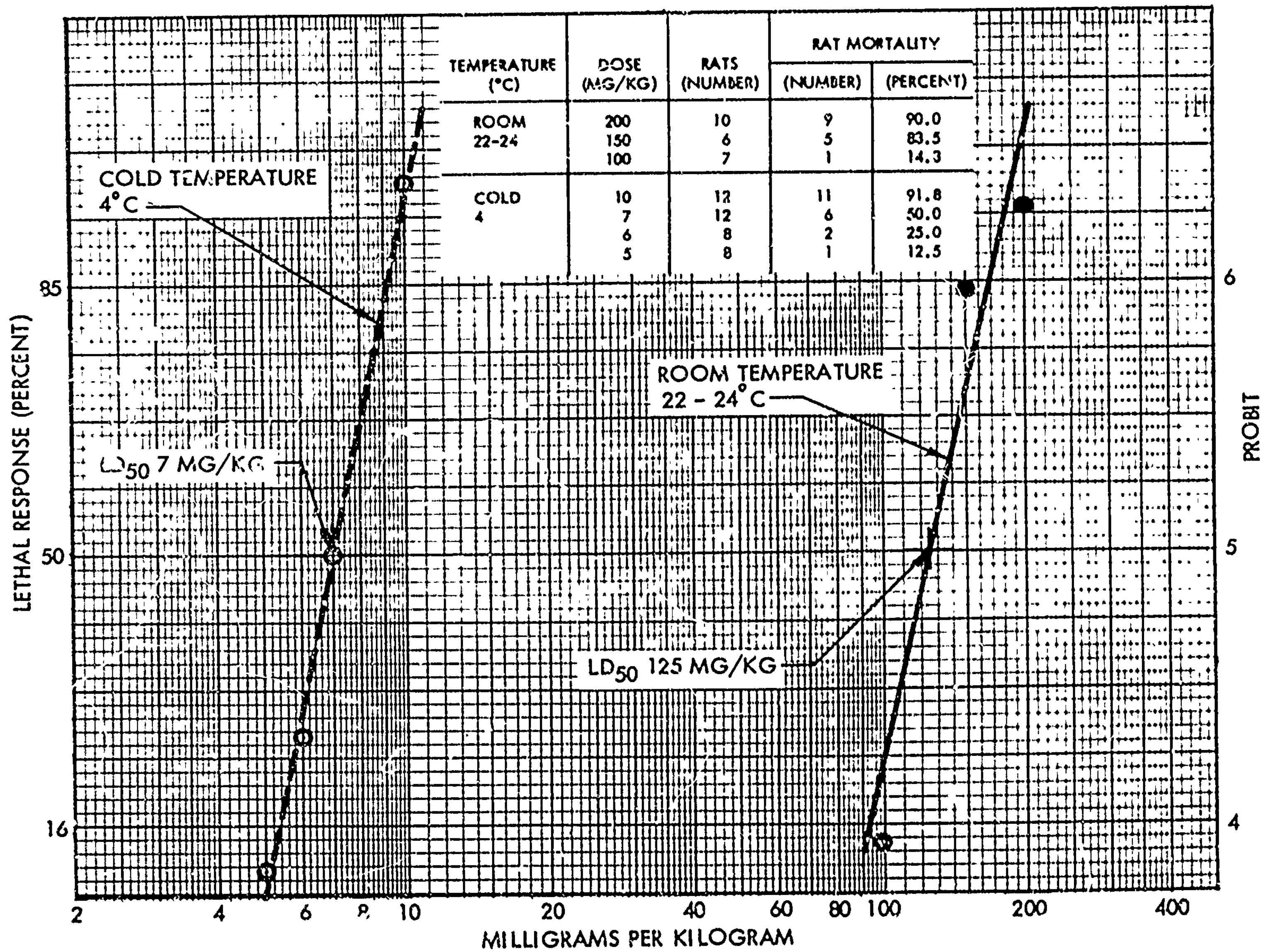
Sleeping in Monkeys Injected Intraperitoneally with Sodium Pentobarbital or with Sodium Pentobarbital and Dextroamphetamine Sulfate Mixture at 23° and 4° C

| Temperature (°C) | Dose (mg/kg) | | No. of Monkeys Used | No. of Monkeys Asleep |
|---|---|---|---|---|
| | Pentobarbital | Dextroamphetamine | | |
| Room 23 | 15 | 0.2 | 3 | 1 |
| | 15 | - | 2 | 2 |
| Cold 4 | 40 | 1.0 | 2 | 2 |
| | 40 | - | 2 | 2 |
| | 20 | 0.5 | 3 | 2 |
| | 20 | - | 2 | 2 |
| | 15 | 0.2 | 3 | 1 |
| | 15 | - | 2 | 2 |

Prochlorperazine

Prochlorperazine ethanesulfonate powder was dissolved in saline and injected intraperitoneally into rats. The results are presented as prochlorperazine base. Figure 7 shows the responses of several groups of rats. The $LD_{50}$ was 125 mg/kg at 22° to 24° C and 7 mg/kg at 4° C. The intraperitoneal toxicity of prochlorperazine was about 18 times greater at 4° C than at 22° to 24° C.

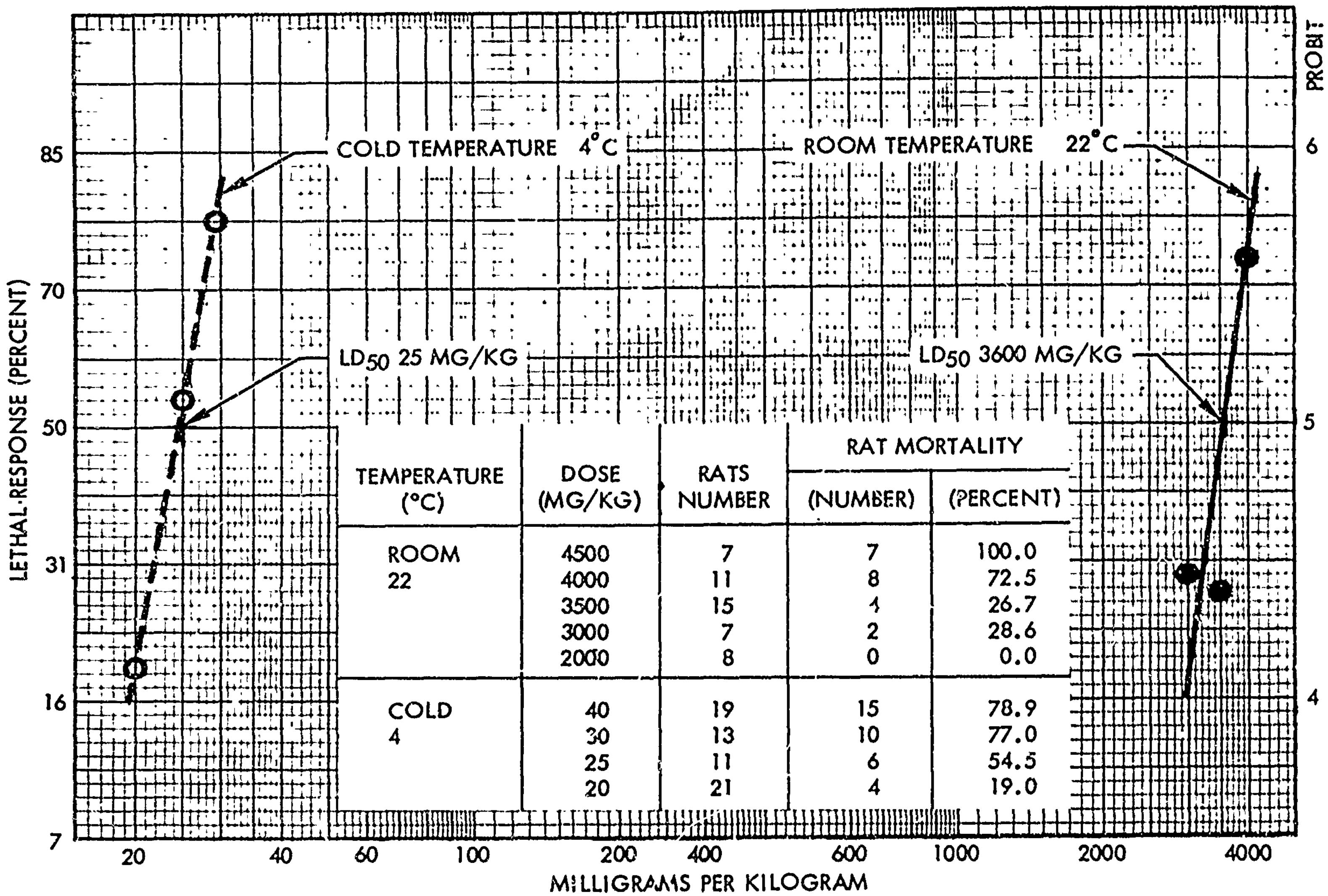
Prochlorperazine dimaleate, suspended in a vehicle of gum arabic and water, was used for the acute oral toxicity study in rats. Figure 8 shows the




| TEMPERATURE (°C) | DOSE (MG/KG) | RATS (NUMBER) | RAT MORTALITY (NUMBER) | RAT MORTALITY (PERCENT) |
|---|---|---|---|---|
| ROOM 22-24 | 200 | 10 | 9 | 90.0 |
| | 150 | 6 | 5 | 83.5 |
| | 100 | 7 | 1 | 14.3 |
| COLD 4 | 10 | 12 | 11 | 91.8 |
| | 7 | 12 | 6 | 50.0 |
| | 6 | 8 | 2 | 25.0 |
| | 5 | 8 | 1 | 12.5 |

FIGURE 7

Lethal Response of Rats to Intraperitoneal Injections of Prochlorperazine (Base) at Room Temperature and at $4^{\circ}$ C




| TEMPERATURE (°C) | DOSE (MG/KG) | RATS NUMBER | RAT MORTALITY (NUMBER) | RAT MORTALITY (PERCENT) |
|---|---|---|---|---|
| ROOM 22 | 4500 | 7 | 7 | 100.0 |
| | 4000 | 11 | 8 | 72.5 |
| | 3500 | 15 | 4 | 26.7 |
| | 3000 | 7 | 2 | 28.6 |
| | 2000 | 8 | 0 | 0.0 |
| COLD 4 | 40 | 19 | 15 | 78.9 |
| | 30 | 13 | 10 | 77.0 |
| | 25 | 11 | 6 | 54.5 |
| | 20 | 21 | 4 | 19.0 |

FIGURE 8

Lethal Responses of Rats to Oral Intubation of Prochlorperazine Dimaleate (Compazine)

oral $LD_{50}$ to be 3600 mg/kg at 22° C and 25 mg/kg at 4° C. The oral toxicity of prochlorperazine dimaleate was about 144 times greater at 4° C than at 22° C.

High doses of prochlorperazine ethanesulfonate were injected intraperitoneally into monkeys to seek a lethal dose level. These monkeys had been used at weekly or 10-day intervals for the present series of tests with dextroamphetamine, pentobarbital, and with prochlorperazine on the response to electric shock. With such monkeys, an intraperitoneal dose of 300 mg/kg of prochlorperazine base was lethal at room temperature, while 120 mg/kg was lethal after three hours at 4° C. These results, however, are not to be taken as indicative of the lethal response to a single dose of prochlorperazine if it were injected into untreated monkeys. During these various tests, it appeared that the monkeys were developing a tolerance to the drug in that the period of tranquilization was not extended by increasing the dosage. The monkeys were usually tranquilized in 5 to 10 minutes and, in spite of the increased dose, became belligerent again two to three hours after injection.

Several tests with dogs receiving successive intraperitoneal injections of 6, 18, 24 and 50 mg of prochlorperazine as base every 10 days at 4° C and at room temperature did not reveal a lethal dose. It is possible that the dogs developed a tolerance as did the monkeys.

To seek a possible reason for death of the rats subjected to prochlorperazine by intubation, several groups of rats were given various doses of prochlorperazine dimaleate suspension. Rectal temperatures were taken at hourly intervals. The results are shown in Figure 9. At 22° to 24° C there were equal average drops in rectal temperature in response to doses of 3500 and 350 mg/kg, with smaller effects at 40 and 20 mg/kg. At 4° C, the response to 40 mg/kg was quite marked, the average drop being about 12° C in seven hours, with death in six of seven rats after eight hours. At 4° C, the response to 20 mg/kg was not great, the average drop being about 2° C in seven hours, with no deaths after eight hours. It appears possible that in the cold environment death was due to the combined effect of the cold and the lowering of body temperature by the hypothermic action of the drug. This would result in a loss of the ability of the temperature center to maintain or permit the body to compensate for the lowered temperature.

Incidentally, an autopsy of several rats eight hours after being given a dose of 3500 mg/kg showed retention of the suspension in the stomach and intestines. With 350 mg/kg, only a small amount of residue was seen in the small intestines. No other macroscopic changes were observed in the viscera of the thorax or abdomen.

Table III shows the avoidance responses of five rhesus monkeys to a mild electric shock at 22° to 24° C and after three hours at 4° C when injected intraperitoneally with prochlorperazine ethanesulfonate. Injections of

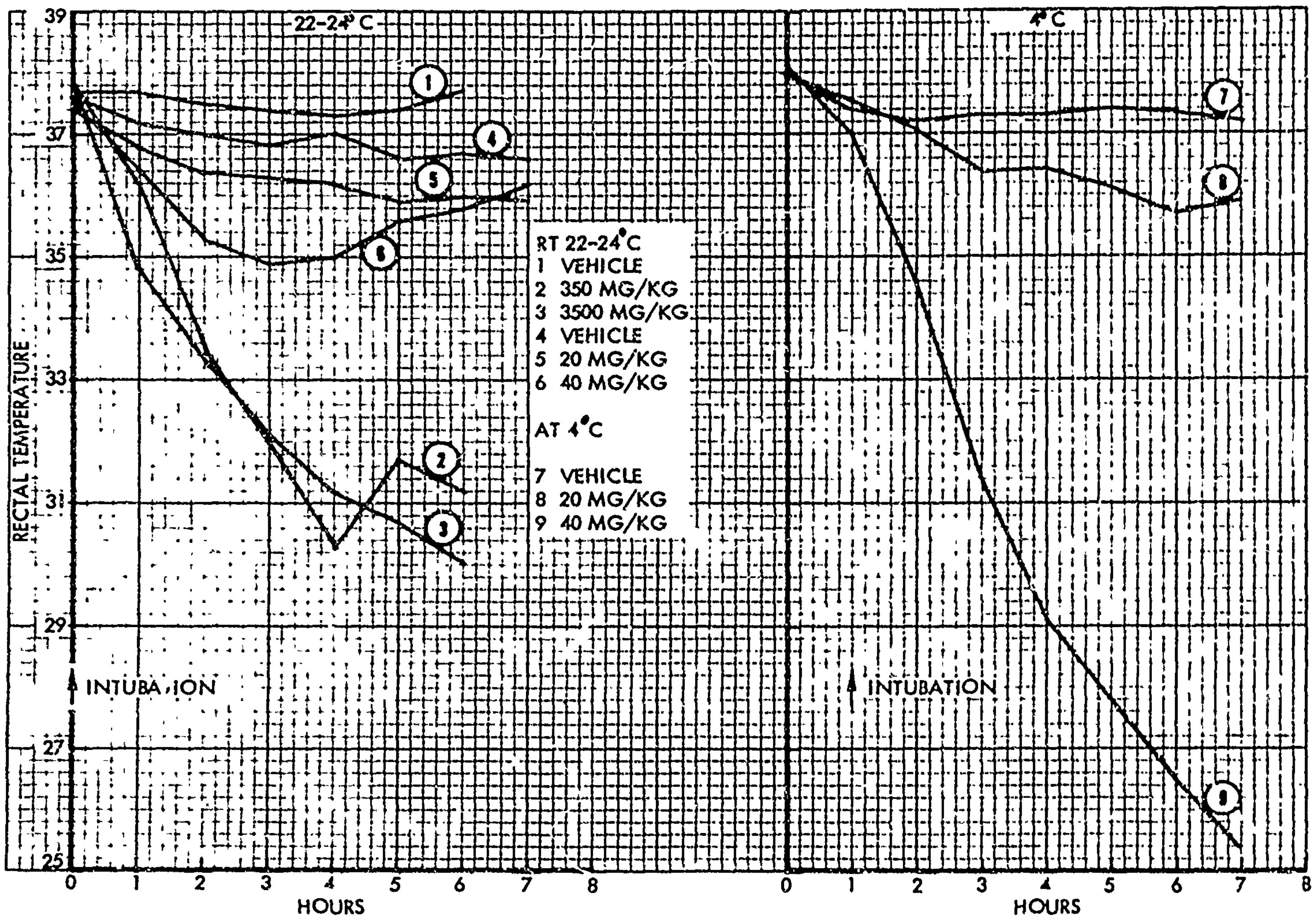



FIGURE 9

Relation of Oral Dose of Prochlorperazine Dimaleate Suspension to Rectal Temperature of Rats at Room Temperature and at 4° C

TABLE III

Avoidance Response in Monkeys Injected Intraperitoneally with Prochlorperazine and Subjected to a Mild Electric Shock at 22° to 24° C and at 4° C

| Temperature (°C) | Dose* (mg/kg) | No. of Tests | Avoidance |
|---|---|---|---|
| Room | 0.60 | 1 | 0 |
| 22 to 24 | 0.10 | 2 | 1 |
| | 0.05 | 2 | 0 |
| | 0.04 | 1 | 0 |
| | 0.02 | 2 | 2 |
| Cold | 0.60 | 1 | 0 |
| 4 | 0.30 | 1 | 0 |
| | 0.20 | 1 | 0 |
| | 0.10 | 1 | 0 |
| | 0.05 | 1 | 0 |
| | 0.02 | 4 | 4 |

*Dosage is given as the base of prochlorperazine ethanesulfonate

0.2 mg/kg were inadequate to tranquilize the monkeys; they were able to avoid an electric shock at either environment. Doses of 0.04 and 0.05 mg/kg or more did tranquilize the animals both in the cold and at room temperature.

The effect of intraperitoneal injections of prochlorperazine ethanesulfonate in preventing emesis in dogs to a subcutaneous injection of apomorphine is shown in Table IV. At 22° to 24° C, a dose of 0.6 mg/kg was about as effective as a dose of 0.4 mg/kg at 4° C. Considering the number of tests involved, prochlorperazine was equally effective in preventing apomorphine emesis at either environment.

## IV

## SUMMARY

The subcutaneous acute toxic dose of meperidine hydrochloride (Demerol) for rats was about twice as great at 4° C ($LD_{50}$ 70 mg/kg) as at 22° to 24° C ($LD_{50}$ 125 mg/kg). The subcutaneous analgesic doses were about 2.5 to 5

TABLE IV

Inhibition of Apomorphine Emesis in Dogs Injected Intraperitoneally with Prochlorperazine at 22° to 24° C and at 4° C

| Temperature (°C) | Dose (mg/kg) | No. of Tests | Emesis |
|---|---|---|---|
| Room | 0.6 | 4 | 2 |
| 22 to 24 | 0.4 | 4 | 4 |
| | 0.2 | 4 | 4 |
| Cold | 1.0 | 4 | 0 |
| 4 | 0.8 | 4 | 1 |
| | 0.6 | 6 | 2 |
| | 0.4 | 10 | 5 |
| | 0.2 | 4 | 4 |

times as effective at 4° C as at 21° C. A therapeutic index of 8.8 at 4° C and of 6.3 at 21° C was calculated.

Dextroamphetamine sulfate (Dexedrine), injected subcutaneously was 7.5 times more toxic for rats subjected to 4° C than for rats kept at room temperature ($LD_{50}$ at 23° C 240 mg/kg and at 4° C 32 mg/kg). In dogs the acute toxicity did not differ greatly at room temperature or cold environments. The sleep response in monkeys at both environments was inhibited by a dose of 0.2 mg/kg of dextroamphetamine sulfate injected intraperitoneally along with 15 mg/kg of pentobarbital.

Prochlorperazine ethanesulfonate (Compazine) was 18 times more toxic for rats injected intraperitoneally at 4° C than for those at 22° to 24° C ($LD_{50}$ as base at 22° to 24° C 125 mg/kg and at 4° C 7 mg/kg). With a suspension of prochlorperazine dimaleate administered orally, the ratio of acute toxicity in rats was 144 to 1 ($LD_{50}$ at 22° C 3600 mg/kg and at 4° C 25 mg/kg). Rectal temperatures were taken hourly on another series of rats given a suspension of prochlorperazine dimaleate at 4° C and at room temperature. It was concluded that the lethal response at 4° C could have been due to an additive effect of the hypothermic action of the drug and of the cold environment to a point where the temperature center was no longer operative. Monkeys, which had been used in previous tests with various drugs, appeared to have become tolerant to increasing doses of prochlorperazine. The avoidance responses of five rhesus monkeys injected intraperitoneally and subjected to a mild electric shock was designed to test tranquilization by the drug. Doses

of 0.04 to 0.05 mg/kg or more tranquilized the monkeys both in the cold and at room temperature. In dogs, intraperitoneal injections of prochlorperazine ethanesulfonate at $22^{o}$ to $24^{o}$ C (0.6 mg/kg) were about as effective as at $4^{o}$ C (0.4 mg/kg) in preventing emesis by an emetic dose of apomorphine.

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13. ABSTRACT In rats acutely exposed to cold as compared to room temperature, the toxic responses to parenteral injections of meperidine hydrochloride, of dextroamphetamine sulfate and of prochlorperazine ethanesulfonate were invariably greater in cold than at room temperature. With further experiments an even greater increase was noted in the acute oral toxicity of prochlorperazine dimaleate at 4° C; the acute oral toxicity of this drug was 144 times greater at 4° C than at room temperature. This large difference in toxicity appeared to be an additive effect of the inherent hypothermic action of the drug and of the temperature-lowering action in the cold environment. Tests with larger animals, monkeys and dogs, indicated that the differences in toxicity between the room temperature and cold environments were not as great as in rats. The ability of large animals to retain body heat in the cold for a longer time than rats can may have contributed to the lesser effect. The results with monkeys injected with prochlorperazine in increasing dosage may have revealed the possibility of a tolerance development to the drug. Dextroamphetamine sulfate was about equally effective at either environment in inhibiting sleep in monkeys induced with pentobarbital. The tranquilizing effect of prochlorperazine, as shown by avoidance behavior in monkeys subjected to a mild electric shock, was found to be about the same at 4° C as at room temperature. In dogs, injections of prochlorperazine at room temperature were about as effective as at 4° C in preventing emesis by an emetic dose of apomorphine.

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| Cold-exposed animals | | | | | | |
| Therapeutic drugs | | | | | | |
| Prochlorperazine | | | | | | |
| Dextroamphetamine sulfate | | | | | | |
| Meperidine hydrochloride | | | | | | |
| Acute toxicity | | | | | | |
| Avoidance response | | | | | | |

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